PATENT

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Applicant(s):	Abad *et al.*	
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Examiner:	Kubelik, Anne R.	
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REPLY BRIEF UNDER 37 C.F.R. § 1.193(b)(1)

This Reply Brief is filed pursuant to 37 CFR § 1.193(b)(1) and is filed in response to the Examiner's Answer of December 23, 2005, the Examiner's Answer being in response to an Appeal Brief filed September 6, 2005.

APPELLANTS' CLAIMED INVENTION MEETS THE REQUIREMENTS FOR PATENTABILITY

Generally, the pending claims rejected by the Examiner are drawn to an isolated nucleic acid comprising a nucleotide sequence having at least 90%, at least 93%, at least 94%, and at least 95% sequence identity to SEQ ID NO:1; transformed plants comprising the nucleotide sequences having at least 90%, at least 93%, at least 94%, and at least 95% sequence identity to SEQ ID NO:1; and, methods for impacting an insect pest comprising introducing into a plant or cell at least one nucleotide construct comprising a nucleotide sequence having at least 90%, at least 93%, at least 94%, and at least 95% sequence identity to SEQ ID NO:1. It is noted that the claims drawn to SEQ ID NO:1 or to a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO:2 have been deemed allowable if rewritten in independent form.

Claims 1-3, 9-12, 17-19, 43, 46, 49, 52, and 55-64 stand rejected under 35 U.S.C. § 112, first paragraph as not enabled and lacking written description. As discussed in more detail below, the specification meets the requirements of 35 U.S.C. § 112 and fully describes and enables the rejected claims. Thus, it is respectfully requested that the rejections be reversed.

I. THE CLAIMED INVENTION MEETS THE REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH, FOR ENABLEMENT

The Examiner has rejected the claims under 35 U.S.C. § 112, first paragraph, and indicated that the specification, while being enabling for nucleic acids encoding SEQ ID NO:2 and 10, expression cassettes comprising the nucleic acids, plants and seeds comprising a construct comprising the nucleic acid, and a method of using it to impact a plant pest, does not reasonably provide enablement for any nucleic acid that has 90% identity to SEQ ID NO:1. For the following reasons, the Examiner's reasoning is not well founded and ignores the guidance provided in the specification and in the art, and the rejection should be reversed.

The specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371, 52 U.S.P.Q.2d (BNA) 1129, 1135 (Fed. Cir. 1999); *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d (BNA) 1001, 1004 (Fed. Cir. 1997); *PPG Inds., Inc. v. Guardian Inds. Corp.*, 75 F.3d 1558, 1564, 37 U.S.P.Q.2d (BNA) 1618, 1623 (Fed. Cir. 1996); *In re Wright*, 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d (BNA) 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 495-96, 20 U.S.P.Q.2d (BNA) 1438, 1444-45 (Fed. Cir. 1991). "That some experimentation may be required is not fatal, the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d at 495, 20 U.S.P.Q.2d (BNA) at 1444. The enablement section of 35 U.S.C. § 112, first paragraph, "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970). In order to determine whether the present claims are enabled, an analysis of the teachings of the specification must be performed as well as an inquiry

into the knowledge of persons of ordinary skill in the art. *In re Bowen*, 492 F.2d 859, 861, 181 U.S.P.Q. (BNA) 48, 50 (C.C.P.A. 1974).

A. The Claimed Invention is Fully Taught in the Specification

The claimed sequences have identity to SEQ ID NO:1 and in addition require that the nucleotide sequences encode a polypeptide that is pesticidal for at least one pest belonging to the order Coleoptera. The specification teaches those skilled in the art how to make the claimed nucleotide sequences and provides examples of such sequences. The specification provides: nucleotide sequences that fall within the scope of the claims (see, for example, pp. 11, 12, 13, 14, 18, 19, 25, and 65); guidance regarding alterations that allow the amino acid sequence to retain pesticidal activity (see, for example, p. 18 and pp. 19-20); methods for assaying the pesticidal activity of proteins (pp. 8 and 29, Example 4, Example 6, and Example 7); a discussion of Cry-8-like δ-endotoxins (SEQ ID NO:2 is a Cry-8-like δ-endotoxin) (pp. 24-25); guidance for determining percent identity of sequences (pp. 33-38); and, specific mutations that fall within the scope of the claimed invention (Example 4 and Example 6).

The specification provides multiple truncated variants of SEQ ID NO: 1 and demonstrates that these truncated variants retrain activity. These sequences and the various methods for making and testing activity are discussed in Applicants' Appeal Brief. However, for convenience, a summary of the sequences presented in the application and discussed in the Appeal Brief are provided below in Table 1. Briefly, SEQ ID NO:1 encodes the amino acid sequence set forth in SEQ ID NO:2. Active variants of SEQ ID NO:1 are set forth in SEQ ID NOS: 3, 15, 19, 11, 23, 31, 33, 29, 9, 43, 21, 39, 41, and, 45. SEQ ID NO:3 comprises a full length active variant of SEQ ID NO:1 and shares 92% sequence identity across the full length of SEQ ID NO:1. The remaining active variants are truncates of SEQ ID NO:1. For each truncated active variant, Table 1 provides both the global percent identity of the variant polynucleotide across the full length of SEQ ID NO:1 and a local percent identity across only the region of the truncate which shares homology to SEQ ID NO:1.

The specification provides fourteen (14) active variants of SEQ ID NO:1 which share between 38% and 92% identity across the full length of SEQ ID NO:1. When local alignments

are preformed between the truncated active variants and nucleotides 1 to 2097 of SEQ ID NO:1, the percent identity of the active variants to SEQ ID NO:1 ranges between 100% to 68% sequence identity. As multiple active variants have been provided which have a relationship to SEQ ID NO:1 well below the percent identities recited in the instant claims, the claims of the present invention are enabled.

While each of the 14 active variants of SEQ ID NO:1 provided in the specification provides clear support for enablement, a brief discussion of the active variants of SEQ ID NO:9 and 19 are provided to further emphasize the extent to which variants have been enabled.

SEQ ID NO:1 comprises 3621 nucleotides. SEQ ID NO:19 comprises 1860 nucleotides of SEQ ID NO:1 and continues to retain activity. The demonstration that such a fragment retains activity clearly illustrates that there is an increased likelihood that an alteration to one or more of the 1,761 additional nucleotides in SEQ ID NO:1 could be altered without disrupting function. Moreover, the specification provides further evidence that even the 1860 nucleotides which are set forth in SEQ ID NO:19 can be altered and still continue to retain activity. The active variant set forth in SEQ ID NO: 9 is the same truncate as SEQ ID NO:19 except that SEQ ID NO:9 contains maize optimized codons. As shown in the table below, SEQ ID NO:9 shares 38% global sequence identity to SEQ ID NO:1 and shares 68% local sequence identity and continues to retain activity. Accordingly, the data in the specification provides clear guidance to one of skill in the art that active variants having at least 90%, at least 93%, at least 95%, and at least 95% sequence percent identity to SEQ ID NO:1 can be readily made.

Table 1

SEQ ID NO for nucleotide sequence	Description	Activity	Overall (global) % identity to SEQ ID NO:1	local % identity to nt 1-2007 of SEQ ID NO:1	Support in specification for activity	Corresponding polypeptide SEQ ID NO	Overall (global) % identity to SEQ ID NO:2	local % identity to aa 1-699 of SEQ ID NO:2
15	Truncated deleted aa 1-699 of SEQ ID NO:2 designated as 1218-1A	Activity against Colorado Potato Beetle	55%	100%	Table 1, page 68	16	56%	100%
19	Truncated deleted aa 48-663 of SEQ ID NO:2 designated as 49PVD	Activity against Colorado Potato Beetle	52%	92.3%	Table 1, pp. 68-69	20	52%	92%
11	Truncated/mutated deleted aa 1-699 of SEQ ID NO:2 with insertion of NGSR after aa 164 designated NGSR 1218-1	Activity against Colorado Potato Beetle, Southern Corn Rootworm	56%	99.4%	Table 1, pp. 68-69; Tables 2-4, pp. 70-71	12	56%	99.4%
23	Truncated/mutated deleted aa 1-667 of SEQ ID NO:2, NGS replaced with LKMS at aa 181 designated LKMS R1218-1	Activity against Southern Corn Rootworm	56%	99.6%	Tables 2-4, pp. 70-71	24	56%	99.6%
31	Truncated/mutated deleted aa 48-663 of SEQ ID NO:2 with LKMS NGSR added at aa 114 designated LKMS N49PVD	Activity against Southern Corn Rootworm	51%	91.4%	Tables 2-4, pp. 70-71	32	51%	91.5%

SEQ ID NO for nucleotide sequence	Description	Activity	Overall (global) % identity to SEQ ID NO:1	local % identity to nt 1-2007 of SEQ ID NO:1	Support in specification for activity	Corresponding polypeptide SEQ ID NO	Overall (global) % identity to SEQ ID NO:2	local % identity to aa 1-699 of SEQ ID NO:2
33	Truncated/mutated deleted aa 48-663 of SEQ ID NO:2 with LKMS introduced at trypsin site designated LKMS R49PVD	Activity against Southern Corn Rootworm	51%	91.6%	Tables 2-4, pp. 70-71	34	60%	91.6%
29	Truncated/mutated deleted aa 48-663 of SEQ ID NO:2 with NGSR added designated NGSR N49PVD	Activity against Southern Corn Rootworm	51%	91.4%	Tables 2-4, pp. 70-71	30	51%	91.5%
9	Truncated having maize optimized codons deleted aa 1-699 of SEQ ID NO:2 designated MO1218-1	Activity against Colorado Potato Beetle	38%	68.1%	Table 1, page 68	10	56%	100%
43	Truncated/mutated deleted aa 1-667 of SEQ ID NO:2, native trypsin site (NGS) is replaced with chymotrypsin site (LRMS) at aa 181 designated LRMS R1218-1	Activity against Coleopteran Pests, data not shown	56%	99.6%	Page 27 of specification, lines 22-25	44	56%	99.6%
21	Truncated/mutated deleted aa 1-667 of SEQ ID NO:2, additional LKMS designated LKMS N1218-1	Activity against Coleopteran Pests, data not shown	56%	99.4%	Page 27 of specification, lines 22-25	22	56%	99.4%

SEQ ID NO for nucleotide sequence	Description	Activity	Overall (global) % identity to SEQ ID NO:1	local % identity to nt 1-2007 of SEQ ID NO:1	Support in specification for activity	Corresponding polypeptide SEQ ID NO	Overall (global) % identity to SEQ ID NO:2	local % identity to aa 1-699 of SEQ ID NO:2
39	Truncated/mutated deleted aa 1-699 of SEQ ID NO:2 with addition of LRNS designated LRNS N1218-1	Activity against Coleopteran Pests, data not shown	56%	99.4%	Page 27 of specification, lines 22-25	40	56%	99.4%
41	Truncated/mutated deleted aa 48-663 of SEQ ID NO:2 with addition of LRMS designated LRMS N49PVD	Activity against Coleopteran Pests, data not shown	51%	91.3%	Page 27 of specification, lines 22-25	42	51%	91.5%
45	Truncated/mutated deleted aa 48-663 of SEQ ID NO:2 with trypsin site replaced with LRMS designated LRMS R49PVD	Activity against Coleopteran Pests, data not shown	51%	91.6%	Page 27 of specification, lines 22-25	46	51%	91.6%
3	Full length variant of SEQ ID NO:1 Designated as *Cry1218-2*	Activity against Coleopteran Pests, data not shown	92%	NA	Page 11, lines 15-19. examples 3 and 4	4	89%	NA

Accordingly, the specification provides exemplary sequences that fall within the scope of the claims as well as adequate guidance regarding making, testing, and identifying sequences that fall within the scope of the claims.

B. The Examiner overlooks the support in the specification and the teachings of the prior art

The Examiner argues repeatedly that the specification provides no guidance for which 362 nucleotides would be altered in a sequence having 90% identity to SEQ ID NO:1, which 253 nucleotides would be altered in a sequence having 93% identity to SEQ ID NO:1, and which 217 nucleotides would be altered in a sequence having 94% identity to SEQ ID NO:1. The Examiner's analysis is improper. As held by the court in *In re Borkowski*, 422 F.2d 904, 909, 164 U.S.P.Q. (BNA) 642, 645 (C.C.P.A. 1970), it is inappropriate "to study appellants' disclosure, to formulate a conclusion as to what he (the Examiner) regards as the broadest invention supported by the disclosure, and then to determine whether appellant's claims are broader than the Examiner's conception of what 'the invention' is." In the present case, the methods and examples disclosed in the specification readily teach one of skill in the art to make and test sequences having at least 90% identity to SEQ ID NO:1.

The specification provides guidance to one of skill in the art for making modifications, describes the domains of the cry protein, and provides insights as to where modifications may be tolerated. See, for example, pages 23 and 24. The specification further teaches preparing modified sequences and testing such sequences for activity. *See*, for example, pages 23, 24, and 29, as well as, Examples 1, 6, and 7. Modified versions and truncated versions of the polypeptide are disclosed retaining pesticidal activity.

The Examiner also ignores the information available in the art as of the filing date regarding δ-endotoxins. As noted in the Appeal Brief, δ-endotoxins are extremely well-characterized and related to various degrees by similarities in their amino acid sequences and tertiary structures. The specification contains a reference to Li *et al.* as well as a discussion on designing mutant sequences. *See*, for example, page 25 of the specification:

> The inventors of the present invention used the solved structure of the *Cry3A* gene (Li *et al.* (1991) *Nature* 353:815-821) to produce a homology model of the Cry8 δ-endotoxin disclosed and claimed herein as SEQ ID NO:2 to gain insight into the relationship between structure and function of the endotoxin, and to design the recombinantly engineered proteins disclosed and claimed herein. A combined consideration of the published structural analyses of *B. thuringiensis* endotoxins and the reported function associated with particular structures, motifs, and the like indicates that specific regions of the endotoxin are correlated with particular functions and discrete steps of the mode of action of the protein. For example, δ-endotoxins isolated from *B. thuringiensis* are generally described as comprising three domains, a seven-helix bundle that is involved in pore formation, a three-sheet domain that has been implicated in receptor binding, and a beta-sandwich motif (Li *et al.* (1991) *Nature*, 305:815-821).
>
> The inventors reasoned that the toxicity of Cry8-like proteins, and specifically the toxicity of the Cry8 protein, could be improved by targeting the region located between alpha helices 3 and 4 of domain 1 of the endotoxin protein. This theory was premised both on the knowledge that alpha helices 4 and 5 of domain 1 of Cry3A δ-endotoxins had been reported to insert into the lipid bilayer of cells lining the midgut of susceptible insects (Gazit *et al.*, (1998) *PNAS USA* 95:12289-12294); the inventors' knowledge of the location of trypsin and chymotrypsin cleavage cites within the amino acid sequence of the wild-type protein; and the observation reported herein that the protein encoded by 1218-1 (i.e., SEQ ID NO:2) was more active against certain Coleopterans following *in vitro* activation by trypsin or chymotrypsin treatment. Accordingly, the inventors engineered a mutant Cry8-like protein that would comprise at least one additional trypsin cleavage site in the region located between helices 3 and 4 of domain 1.

Specification, p. 25, lines 1-24.

Yet, even in view of the description provided in the specification, the many examples taught, and the knowledge available in the art, the Examiner ignores all the teachings and concludes "[t]he instant specification fails to provide guidance for which amino acids of SEQ ID NO:2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain Cry 8 activity of the encoded protein." (Examiner's Answer, page 5). Even in view of Applicants' data demonstrating truncated polypeptides which retain activity in which 1,761 nucleotides have been removed from SEQ ID NO:1 and the encoded protein retains

activity, the Examiner concludes, "[t]he specification also fails to provide guidance for which amino acids can be deleted." (Examiner's Answer, page 5).

The Examiner discounts all the disclosure and teachings and provides no basis for her conclusion. The two references cited by the Examiner support Applicants' position that the claims are enabled, as discussed in more detail below.

Under the facts of the present application, one skilled in the art would understand whether a particular protein has at least 90%, or at least 93%, 94%, or 95% sequence identity with SEQ ID NO:1 as set forth in the claims. In addition, functional assays are disclosed in the specification that provide sufficient guidance for one skilled in the art to determine whether a particular polynucleotide is within the scope of the claims. Thus, the claims are fully enabled.

C. That some experimentation may be necessary does not indicate that the claims are not enabled

It is recognized that in unpredictable art areas, the court has refused to find broad generic claims enabled where the corresponding specifications only demonstrate the enablement of one or very few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim. *See, e.g., In re Goodman*, 11 F.3d 1046, 1050-52, 29 U.S.P.Q.2d (BNA) 2010, 2013-15 (Fed. Cir. 1993); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212-14, 18 U.S.P.Q.2d (BNA) 1016, 1026-28 (Fed. Cir. 1991); *In re Vaeck*, 947 F.2d at 496, 20 U.S.P.Q.2d (BNA) at 1445. The court has explained that enablement is lacking in those cases because the undescribed embodiment cannot be made based on the disclosure in the specification, without undue experimentation. However, the court has made clear that the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. (BNA) 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeal has indicated: "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." *Ex Parte Jackson*, 217 U.S.P.Q. (BNA) 804, 807 (1982).

In the present case, all the Examiner has established is that some experimentation would be required to make and use other embodiments of the claimed invention. What the Examiner has not done is perform the fact-finding needed in order to reach a proper conclusion of undue experimentation. The Examiner has not relied upon any evidence in support of this rejection which would establish that making and testing other sequences beyond those described in the present specification amounts to undue experimentation. In fact, the Examiner has ignored the guidance in the specification, the presence of working examples, the teachings of the prior art, and a declaration by Dr. Abad stating that the procedures described in Examples 4, 6, and 7 for making and testing modified sequences are routine in the art. The Examiner makes the rejection based upon unsupported opinions.

In establishing nonenablement, the burden rests initially with the Examiner to substantiate the unpredictability of the art and that, given the unpredictability, the specification does not provide sufficient information to guide those of skill to make and use the claimed invention across the full scope of the claims. In the present case, a clear goal is disclosed. Furthermore, guidance is provided for making the claimed sequences, assays are provided to determine whether modified sequences would encode proteins that retain activity, examples are provided showing that modifications to the nucleotide sequence can be made and the encoded proteins retain pesticidal activity, and art is cited that provides information on the cry proteins of the invention. Thus, whatever unpredictability surrounds the construction of other sequences, the need for undue experimentation is mitigated by the examples of how to make and use such claimed sequences.

D. The Examiner mischaracterizes the Lazar reference

The Examiner argues that making conservative amino acid substitutions does not produce predictable results and cites Eliane Lazar *et al.*, *Molecular & Cellular Biology* 8:1247-1252 (1988) in support of her position. The Examiner indicates that the conservative substitution of

glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while nonconservative substitutions with alanine or asparagine had no effect. The Examiner fails to consider the entire teachings of the reference.

First, the Lazar reference is drawn to studying transforming growth factor α (TGF-α). TGF-α is a mammalian polypeptide of 50 amino acids. The polypeptide is in no way related to the Cry proteins of the present invention. The reference relating to TGF-α does not bear any relevance to the claimed cry proteins.

Secondly, with respect to the modifications described by Lazar, two amino acids of TGF-α which were known to be conserved among the family of EGF-like polypeptides were modified. It would come as little surprise to one skilled in the art that the modification of such a conserved amino acid should lead to the loss of function described by the authors. One of the changes at position 47 described by the authors indicates that [Asn-47]- TGF-α retains biological activity. The authors note that interestingly, two of the EGF-like viral proteins, myxomal growth factor and Shope fibroma growth factor, have Asn instead of Asp in position 47. Thus, the reference supports Applicants' position that protein domains are important and that by aligning sequences, one of skill in the art can determine what sites would likely tolerate changes.

E. The Examiner mischaracterizes the Hill reference

It appears that the Examiner intended to cite M.A. Hill *et al.*, *Biochemical & Biophysical Research Communications* 244:573-577 (1998) as supporting the position that substitution of a residue with a conservative amino acid can drastically reduce enzyme activity. The Examiner notes that "[s]imilarly, [*sic*] teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the 'nonconservative' amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the 'conservative' amino acid arginine drastically reduced enzyme activity."

First, the Hill reference is drawn to studying ADP-glucose pyrophosphorylase. The polypeptide is in no way related to the Cry proteins of the present invention. The reference relating to ADP-glucose pyrophosphorylase does not bear any relevance to the claimed cry proteins.

Secondly, with respect to the modifications described by Hill, the modified residues were conserved among bacterial and plant ADP-glucose pyrophosphorylases. As set forth in the first line of the abstract, "[t]wo **absolutely conserved** histidines and a third **highly conserved** histidine are noted in 11 bacterial and plant ADP-glucose pyrophosphorylases." (emphasis added) These **absolutely** and **highly conserved** histidines were mutagenized and characterized in the paper. It would come as little surprise to one skilled in the art that the modification of one of these conserved amino acids should lead to the loss of function described by the authors.

F. The Lazar and Hill references supports Applicants' position that it is within the skill of the art to make and test modifications

The Lazar reference published in 1988 and the Hill reference published in 1998, both demonstrate that one of skill in the art well before 2000, the priority date of the present application, could make substitutions in polypeptide sequences and test for activity. Nothing more is required in the present application.

The specification teaches that a comparison of the amino acid sequences of Cry toxins of different specificities reveals five highly conserved sequence blocks. Structurally, the δ-endotoxins comprise three distinct domains, which are, from the N- to C-termini: a cluster of seven alpha- helices implicated in pore formation, three anti-parallel beta sheets implicated in cell binding, and a beta sandwich. *See* page 23 of the specification. The specification further teaches that a truncated protein can be made that retains activity. Whether the protein has 100% identity to the region it shares with SEQ ID NO:1 (as argued by the Examiner) or 55% identity across the entire sequence of SEQ ID NO:1 (as noted by Applicants), the truncated polypeptide would lead one of skill in the art to conclude that the deleted region would likely tolerate modifications. Furthermore, one of skill in the art would appreciate that changes would be more likely to be tolerated outside of conserved domains. Thus, there is teaching in the specification that would guide one of skill in the art in making modifications. The specification further teaches preparing modified sequences and testing such sequences for activity. *See*, for example, pages 23, 24, and 29 as well as Examples 1, 6, and 7.

As assays for determining whether the modified sequences would retain activity were disclosed, one of skill in the art as of the filing date of the present application would have been able to make such modifications and test them for pesticidal activity. Nothing more is required to fully enable the claims.

II. THE CLAIMED INVENTION MEETS THE REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH, FOR WRITTEN DESCRIPTION

In order to satisfy the written description requirement of 35 U.S.C. § 112, the application must reasonably convey to one skilled in the art that the applicant was in possession of the claimed subject matter at the time the application was filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991).

A. The specification contains the necessary structural features to meet the Written Description Requirement

The written description inquiry focuses on whether the specification reasonably conveys to one skilled in the art whether the applicant invented the claimed subject matter. Thus, the relevant inquiries are: What is the applicant's claimed invention? What is now claimed? The claimed invention is directed to nucleotide sequences having specific structural and biological properties. The specification provides both the DNA and amino acid sequences of a representative embodiment of the claimed sequences. Indeed, the Examiner has acknowledged that these claims drawn to specific sequences would be allowable if rewritten as independent claims. The specification also discloses modified sequences that fall within the scope of the claims. Accordingly, the application provides the structural features that characterize nucleic acid sequences having 90%, 93%, 94%, or 95% identity to SEQ ID NO:1 and still retain pesticidal activity. The sequences that fall within the scope of the claims can readily be identified by the methods set forth in the specification.

B. The facts of the present case are distinguishable from Lilly and Fiers

At page 19 of the Examiner's Answer, the Examiner quotes *Eli Lilly* and argues that "[a] single nucleic acid of SEQ ID NO:1 does not constitute a significant portion of the vary large genus of nucleic acids with 90% identity to SEQ ID NO:1." First, as noted above, the specification provides more information than merely reciting SEQ ID NO:1. The specification provides: nucleotide sequence that fall within the scope of the claims (see, for example, pp. 11, 12, 13, 14, 18, 19, 25, and 65) guidance regarding alterations that allow the amino acid sequence to retain pesticidal activity (see, for example, p. 18 and pp.19-20); methods for assaying the pesticidal activity of proteins (pp. 8 and 29, Example 4, Example 6, and Example 7); a discussion of Cry-8-like δ-endotoxins (SEQ ID NO:2 is a Cry-8-like δ-endotoxin) (pp. 24-25); guidance for determining percent identity of sequences (pp. 33-38); and, specific mutations that fall within the scope of the claimed invention (Example 4 and Example 6).

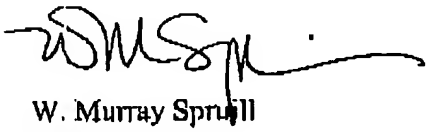
Secondly, the Examiner's appeal to *Eli Lilly* is misplaced. As noted by the Federal Circuit in *Invitrogen Corp. v. Clontech Laboratories, Inc.* 77 U.S.P.Q.2d (BNA) 1161, 1175 (Fed. Cir. 2005), "[i]n those cases . . . , *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d (BNA) 1398 (Fed. Cir. 1997) and *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 U.S.P.Q.2d (BNA) 1601, 1606 (Fed. Cir. 1993), the patent specifications at issue did not identify the sequence (structure) of any embodiment of DNA claimed therein. . . . In contrast, the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features--DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient." *Id.* at 1073.

In the present application, a representative nucleic acid and amino acid sequence is provided. Additionally, modified sequences are disclosed which are representative of the claimed sequences. Accordingly, the application meets the requirement for written description for the claimed sequences.

CONCLUSION

Appellants maintain that the Examiner has failed to carry her burden of establishing that the claims are not patentable because she has (a) failed to establish that it would require undue experimentation to practice the claimed invention and (b) failed to prove that the application does not adequately describe the claimed invention. For these reasons, presented in detail in the Reply Brief, Appellants respectfully requests that the rejections be reversed.

Respectfully submitted,



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